Investigations in the 3,4-Dihydrocoumarin Melilotic Acid Series

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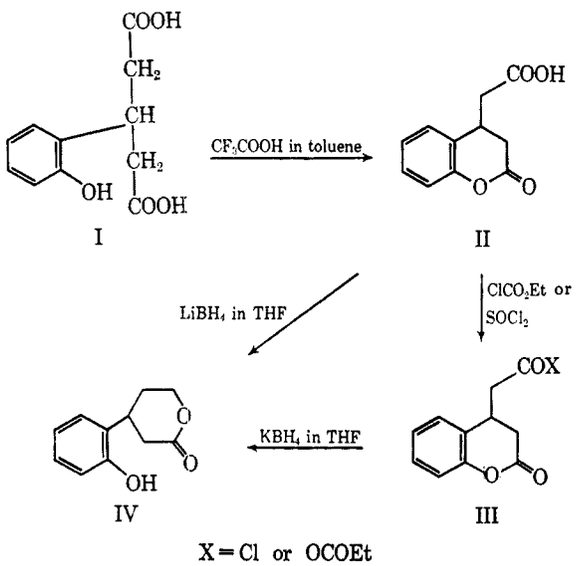
Selective reduction of 3,4-dihydrocoumarin-4-acetic acid (II) leads to 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) by either one of the described two methods. Lactonization of the intermediate 4-hydroxycarboxylic acid to form the above δ-carboxylic acid lactone is preferred over the formation of the phenolic lactone 3,4-dihydro-4-(β-hydroxyethyl)coumarin (XVI). Electrophilic reagents convert 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) into 4-substituted 3,4-dihydrocoumarins. The phenolic lactone 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII), reacts with primary or secondary amine to form 4-substituted chroman derivatives.

Although a great number of natural products related to coumarin are known[1] and coumarins can be characterized by reduction to dihydrocoumarins, relatively little work has been done on 3,4-dihydrocoumarins.[2]

Dihydrocoumarins are hydrolyzed to acids, like melilotic acid (*o*-hydroxyhydrocinnamic acid) which does not cyclize at room temperature to dihydrocoumarin. A number of theories on the biosynthesis and metabolism of coumarin have been proposed which indicate that opening of the heterocyclic ring of coumarin takes place readily, giving rise to melilotic acid as an important product of the coumarin metabolism.[3]

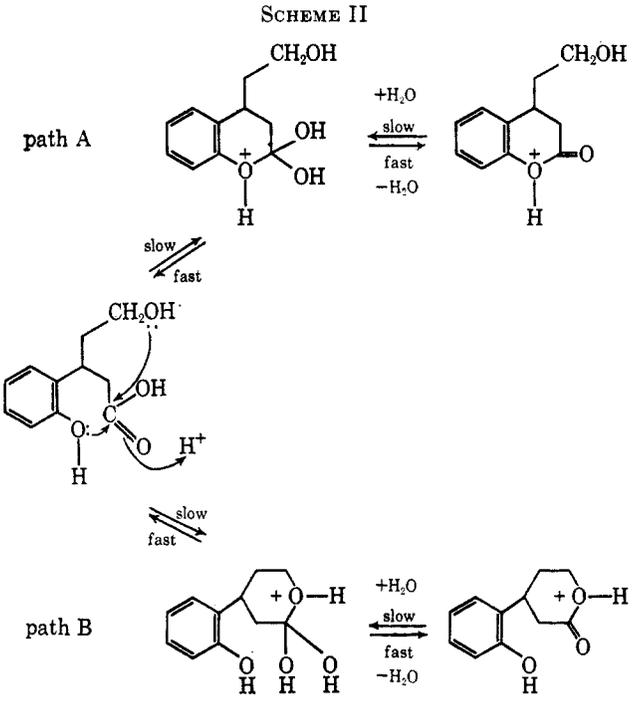
Selective reduction of 3,4-dihydrocoumarin-4-acetic acid, as already reported in a preliminary communication,[4] leads to 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone by either one of the described two methods (Scheme I).

SCHEME I



The rate of acid-catalyzed lactonization reaction of a hydroxy acid bearing a primary alcohol is expected to be faster than that bearing a phenolic hydroxyl, itself an acidic group, particularly in view of the known fact that melilotic acid (*o*-hydroxyhydrocinnamic acid) does not cyclize at room temperature to dihydrocoumarin.[5] Thus, kinetically controlled lactonization should favor formation of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone. Furthermore, the mechanism of the acid-catalyzed lactone formation is pictured as an internal ester formation of the protonated acid and hydroxyl group[6] (Scheme II).

SCHEME II

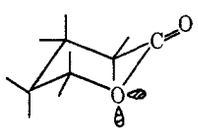


In phenols the delocalization of electrons of the benzene ring is extended to include the OH group. The transition state leading to the dihydrocoumarin system (pathway A) carrying a positive charge on this OH group prevents it from being part of the aromatic system having delocalized electrons. On the other hand, the transition state leading to the δ-lactone will not. Electronic factors should therefore favor formation of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (pathway B).

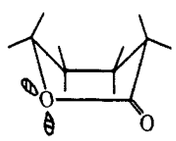
Lemieux[7] considered δ-valerolactone to possess a chair conformation (U) in which the carbonyl group is eclipsed with a *para* orbital of the lone pair of

(1) T. O. Soine, *J. Pharm. Sci.*, **53**, 231 (1964).
(2) For some recent references, see T. Amakasu and K. Sato, *J. Org. Chem.*, **31**, 1433 (1966).
(3) T. Kosuge and E. E. Conn, *J. Biol. Chem.*, **234**, 2133 (1959).
(4) J. A. Vida, *Chem. Ind.* (London), 1344 (1966).
(5) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IV, Part B, Elsevier Publishing Co., The Netherlands, 1959, p 874.
(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 320.
(7) R. U. Lemieux in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 709.

electrons of the ring oxygen. However, Mathieson[8] presented evidence based on X-ray crystallographic analyses that the characteristic shape of the group CC=OOC of a lactone is planar. According to Mathieson, this condition can be satisfied in a six-membered lactone ring by adopting the boat conformation (W).

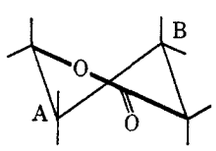


U

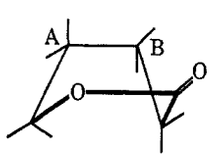


W

In contrast, Overton, *et al.*,[9] have outlined that two conformations satisfy the condition of planarity: (Y) a half-chair conformation having carbon atom A below and carbon atom B above the plane of the lactone function; (Z) a half-boat conformation having carbon atoms A and B displaced to the same side of the plane of the lactone function.



Y



Z

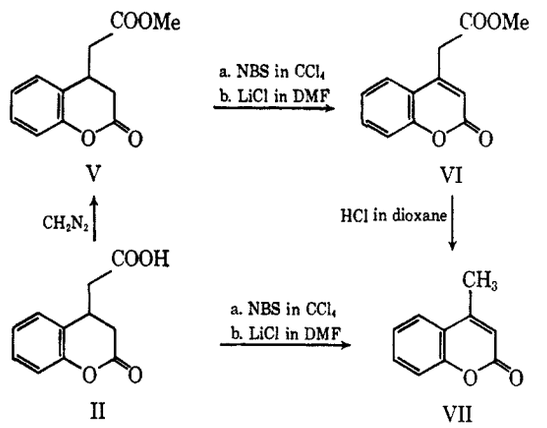
Overton, *et al.*, have suggested that δ-lactones normally adopt the half-chair conformation if other restrictions do not apply. According to Overton, *et al.*, unattached δ-lactones and δ-lactones fused to six-membered saturated carbocyclic rings exist in the half-chair conformation, while δ-lactones fused to five-membered rings exist in the half-boat conformation.

In our case, the δ-lactone, 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, exists in the half-chair conformation and the 3,4-dihydrocoumarin ring probably in the half-boat conformation. Since the half-chair conformation is more stable than the half-boat conformation,[10] formation of the δ-lactone in preference to the dihydrocoumarin ring is sterically favored.

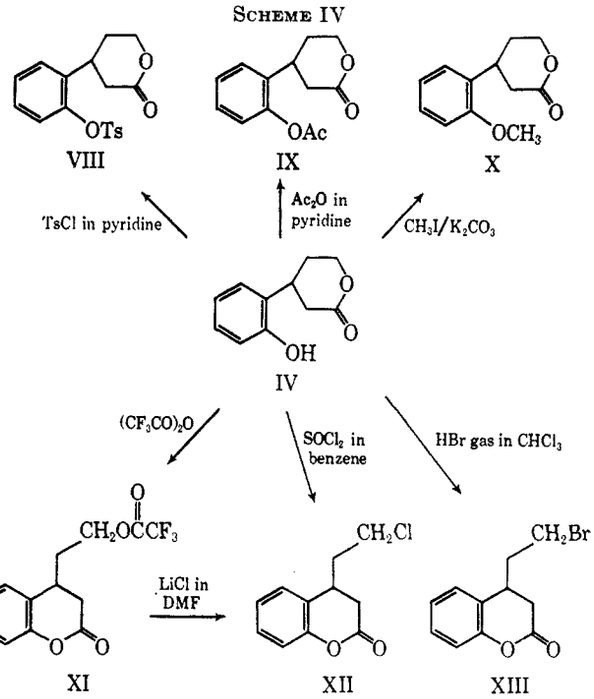
3,4-Dihydrocoumarin-4-acetic acid, upon treatment with diazomethane, was converted into the methyl ester which was brominated and dehydrobrominated to yield 4-carbomethoxymethylcoumarin. Coumarin-4-acetic acids are vinylogs of malonic acid; they lose carbon dioxide at high temperatures; *e.g.*, when the methyl ester was hydrolyzed in boiling aqueous dioxane with hydrochloric acid, the already known 4-methylcoumarin[11,12] was obtained. Similarly the latter compound was obtained from bromination, followed by dehydrobromination of coumarin-4-acetic acid (Scheme III).

Some of the reactions of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone are summarized in Scheme IV.

SCHEME III

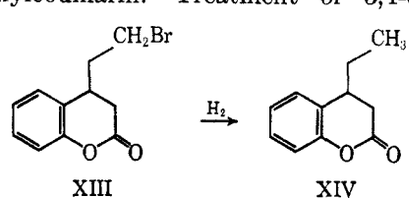


SCHEME IV



Cleavage of the δ-carboxylic acid lactone ring and the subsequent ring closure to form the dihydrocoumarin ring system can be effected with electrophilic reagents, *e.g.*, trifluoroacetic anhydride, thionyl-chloride in benzene,[13] and gaseous hydrobromic acid in chloroform.[14]

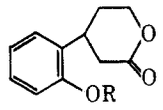
Upon catalytic hydrogenation of 3,4-dihydro-4-(β-bromoethyl)coumarin, there was obtained 3,4-dihydro-4-ethylcoumarin. Treatment of 3,4-dihydro-4-



(β-bromoethyl)coumarin with sodium iodide in a 2:1 mixture of xylene–acetic acid gave a quantitative yield of the 3,4-dihydro-4-(β-iodoethyl)coumarin which in turn could be converted into 3,4-dihydro-4-(β-trifluoroacetoxyethyl)coumarin with silver oxide in

(8) A. M. Mathieson, *Tetrahedron Lett.*, 81 (1963).
(9) K. H. Overton, N. G. Weir, and A. Wylie, *J. Chem. Soc., Sect. C*, 1482 (1966).
(10) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, p 147.
(11) E. H. Woodruff, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., J. Wiley and Sons, Inc., New York, N. Y., 1955, p 581.
(12) C. E. Wheelock, *J. Amer. Chem. Soc.*, **81**, 1348 (1959).
(13) M. Julia, S. Julia, and B. Bemont, *Bull. Soc. Chim. Fr.*, 304 (1960).
(14) R. Lukes and A. Zobacova, *Collection Czech. Chem. Commun.*, **22**, 1849 (1957).

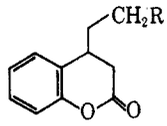
TABLE I[a]



Compound no.	Substituent	Neutral solution				Alkaline solution			
IV	H	280 (2260)	274 (2500)		215 (6300)	293 (3000)	283 (2600)		238 (6400)
X	CH_3	278 (2260)	272 (2480)		218 (7900)		No change		
IX	Ac	268 (254)	262 (281)	255 (261)	208 (8550)	293 (2220)	283 (2700)	276 (2460)	238 (4300)
VIII	Tos	274 (660)	263 (980)	256 (875)	227 (14000)		No change		

[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ).

TABLE II[a]

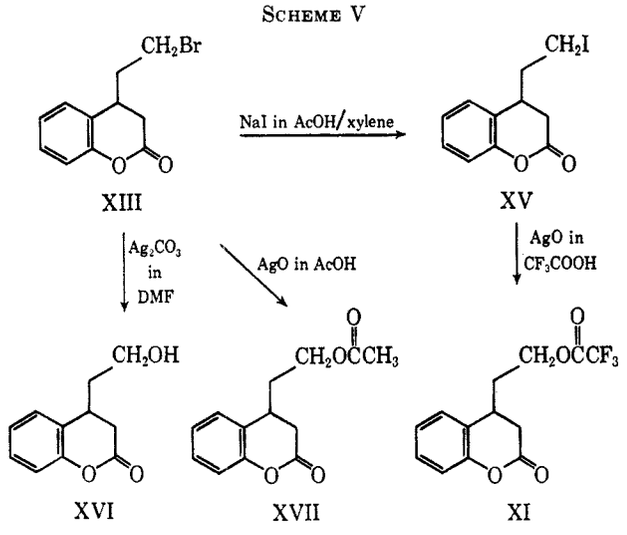


Compound no.	Substituent	Neutral solution				Alkaline solution			
XI	$OCOCF_3$	280 (1080)	273 (1440)	267 (1140)	212 (6120)	293 (2480)	283 (2400)		238 (5570)
XII	Cl	273 (660)	266 (690)	258 (500)	224 (5000)		283 (2400)	276 (2470)	205
XIII	Br	273 (637)	266 (665)	258 (475)	224 (4760)		283 (2360)	276 (2440)	205
XV	I	273 (650)	266 (680)	259 (490)	224 (4775)		283 (2375)	276 (2455)	205
XVI	OH	273 (650)	267 (680)	260 (490)	222 (4900)	293 (1990)	283 (2100)		238 (3780)
XVII	OAc	273 (600)	266 (630)	259 (480)	222 (4500)	293 (1800)	283 (1910)		238 (3600)
XX	NHC_6H_5	283 (2060)	273 (2440)	267 (1990)	220 (8700)	293 (2620)	283 (2270)		237 (7100)

[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ).

trifluoroacetic acid. When 3,4-dihydro-4-(β-bromoethyl)coumarin was treated with silver carbonate in dimethylformamide, 3,4-dihydro-4-(β-hydroxyethyl) coumarin was obtained (Scheme V).

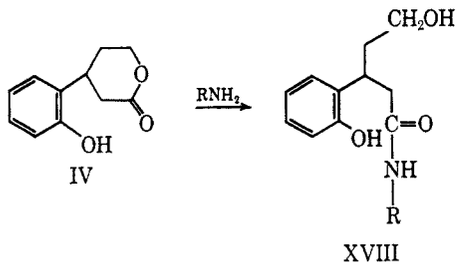
SCHEME V



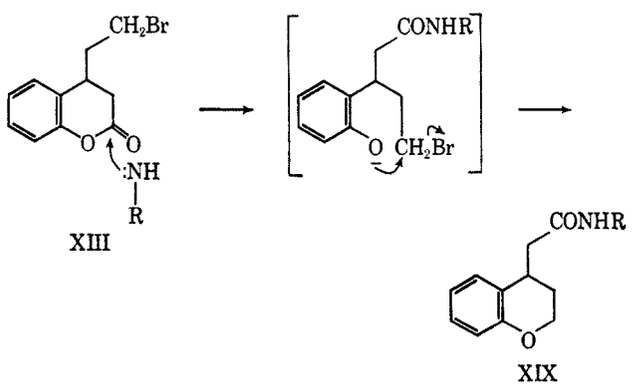
Since the reactions of silver salts with alkyl halides are ordinarily considered[15] to be concerted processes, it is not surprising to find that displacements of the halides proceed with the retention of the 3,4-dihydrocoumarin system.

The reaction of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid with a primary or secondary amine gave amides.

(15) N. Kornblum and D. E. Hardies, *J. Amer. Chem. Soc.*, **88**, 1707 (1966), and references cited therein.

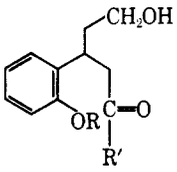


Chromans were the only products isolated from the reaction of 3,4-dihydro-4-(β-bromoethyl)coumarin with a primary or secondary amine, indicating that the nucleophile attacks the lactone carbonyl; *i.e.*, ring opening takes place first with the formation of amide followed by ring closure with the expulsion of the



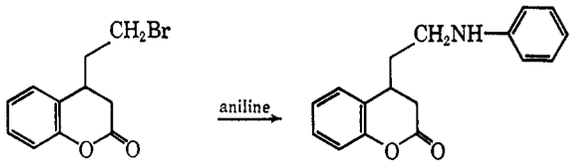
bromide. However, the reaction of 3,4-dihydro-4-dihydro-4-(β-bromoethyl)coumarin with aniline did not lead to the chroman ring system; nucleophilic substitution took place instead, a result which can be explained by the diminished nucleophilicity of aniline compared to a primary or secondary aliphatic amine.

TABLE III[a]



Compound no.[b]	Substituent R′	Substituent R	Neutral solution				Alkaline solution		
XVIIIc	H	$NHCH_2C_6H_5$	280 (1930)	274 (2140)		206 (16100)	293 (2780)		238 (5350)
XVIIId	H	NHC_6H_{11}	280 (1820)	274 (2000)		215 (5950)	293 (2640)	283 (1640)	238 (4820)
XVIIIa	H	NC_5H_{10}	280 (1580)	274 (1740)		209 (10400)	293 (1820)	283 (1640)	238 (3300)
XVIIIb	TOS	NC_5H_{10}	274 (635)	263 (975)	256 (850)	226 (15300)		No change	

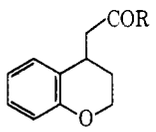
[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ). [b] See Experimental Section.



XIII XX

The ultraviolet absorption data are summarized in Tables I–IV. The highly reactive 4-(β-halogenoethyl)-3,4-dihydrocoumarins show ultraviolet absorption representative of the dihydrocoumarin system[16] in neutral solution; on addition of a few drops of dilute sodium hydroxide solution, immediate change of the spectra revealed the newly formed chroman system.[17]

TABLE IV[a]

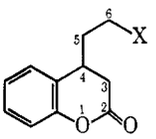


Compound no.[b]	Substituent	Neutral and alkaline solution		
XIXa	$NHCH_2C_6H_5$	283 (2300)	276 (2380)	220 (5,850)
XIXb	NHC_6H_{11}	283 (2200)	276 (2250)	220 (5,900)
XIXc	NC_5H_{10}	283 (2470)	276 (2520)	220 (11,500)
XIXd	$N(C_2H_5)_2$	283 (2470)	276 (2520)	220 (8,900)
XXI	OH	283 (2400)	276 (2520)	218 (6,750)
XXII	OCH_3	283 (2450)	276 (2550)	218 (7,000)

[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ). [b] See Experimental Section.

The nmr spectra are summarized in Tables V–VII. The appearance of the aromatic regions for the three groups of compounds are markedly different, but very similar within one group. This provided an easy method for categorizing other compounds having similar structures. Chemical shifts characteristic of certain groups were used for the structural assignments. Thus a sharp singlet in $CDCl_3$ at 139 cps corresponding to three protons characteristic of acetates attached to phenyl groups established the δ-lactone structure of compound IX (Table VII). A doublet in DMSO-d_6 at 462.2 cps, J = 7.6 cps, of compound XIX, R = C_6H_{11}, and a signal at 302 cps in $CDCl_3$ and at 508 cps in DMSO-d_6 of compound XIX, R = $CH_2C_6H_5$ (Table VI), is characteristic of an amide rather than an amine proton, thus establishing the chroman structure. The familiar pattern of ethyl group of compound XIV established the dihydrocoumarin system (Table V). It was also found that the signals of aromatic protons in the dihydrocoumarin and chroman systems are relatively insensitive to solvent or substituent changes, while in the δ-lactone the pattern is influenced by both solvent and substituent changes.

TABLE V[a]



Substituent	Solvent	C-3	C-4	C-5	C-6
OH	DMSO-d_6	174	194	111	248
$OCOCH_3$	$CDCl_3$	169	188	115	246.2
$OCOCH_3$	DMSO-d_6	175	193	109.4	241.6
H	$CDCl_3$	168	200	98	107.5
$OCOCF_3$	DMSO-d_6	176	195	118.2	266
Cl	$CDCl_3$	170	200	120	212
Br	$CDCl_3$	170	200	125	203
I	$CDCl_3$	170	200	122	189
NHC_6H_5	$CDCl_3$	155	210	126	217

[a] Centers of multiplets, in cycles per second, for protons on indicated carbon.

Experimental Section[18,19]

2-*o*-Hydroxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IV). A.—To the solution of 10.0 g (0.05 mol) of 3,4-dihydrocoumarin-4-acetic acid (II)[4] in 50 ml of benzene 16.4 g (10 ml) of thionyl chloride was added and the solution was refluxed for 2 hr. The excess reagent and the solvent was evaporated under reduced pressure. Benzene (100 ml) was added to the oil and the solvent was evaporated under reduced pressure. The oily residue III was dissolved in 100 ml of dry tetrahydrofuran and 10 g (0.2 mol) of potassium borohydride was added. The reaction mixture was refluxed for 2 hr with stirring. The solvent was evaporated under reduced pressure, 100 ml of 2 *N* hydrochloric acid solution was added to the precooled residue, and the mixture was allowed to stand over-

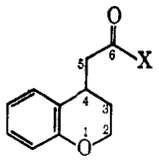
(16) R. H. Goodwin and B. M. Pollock, *Arch. Biochem. Biophys.*, **49**, 1 (1954).

(17) T. J. Webb, *et al.*, *J. Org. Chem.*, **4**, 389 (1939).

(18) Melting points were taken on a Fisher-Johns hot stage and are corrected. Ultraviolet absorption spectra were determined in methanol on a Cary Model 14 recording spectrophotometer. Infrared spectra were recorded on a Beckman IR-7 spectrophotometer and on a Perkin-Elmer Infracord. The nmr spectra[19] were run on a Varian Associates DA-60 spectrometer in deuteriochloroform ($CDCl_3$) or deuteriodimethyl sulfoxide (DMSO-d_6) using tetramethylsilane as internal reference. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Chromatographic separations were done with silica gel, Davison Type 923, 100–200 mesh.

(19) We thank Dr. T. A. Wittstruck for the nmr spectra.

TABLE VI[a]



Substituent	Solvent	C-2	C-3	C-4	C-5[b]		
OH	$CDCl_3$	251.4	122	200.4	153.1 (9.6)	170.5 (4.8)	[−16.0]
OH	DMSO-d_6	247.4	114	192	146.9 (9.4)	162.1 (5.0)	[−16.0]
$N(C_2H_5)_2$	$CDCl_3$	251.2	123	205.2	150.4 (9.0)	162.8 (5.2)	[−15.0]
$N(C_2H_5)_2$	DMSO-d_6	247.2	111	194	...	...	
NHC_6H_{11}	$CDCl_3$	248.8	...	203	136.5 (8.4)	154.1 (6.0)	[−14.4]
NHC_6H_{11}	DMSO-d_6	246.8	...	190.2	133.1 (9.4)	149.3 (5.4)	[−14.2]
OCH_3	DMSO-d_6	247.0	114	193	151.0 (9.4)	167.0 (4.8)	[−15.0]
NC_5H_{10}	DMSO-d_6	247.2	112	...	151.5 (10.0)	161.9 (5.4)	[−15.8]
$NHCH_2C_6H_5$	$CDCl_3$	251.6	122	202	...	...	
$NHCH_2C_6H_5$	DMSO-d_6	247.8	115	194	...	...	

[a] Centers of multiplets, in cycles per second, for protons on indicated carbon. [b] Calculated chemical shift, followed by coupling constant with C-4 proton. The geminal coupling constant is given in brackets. In certain cases the entry is left blank because that portion of the spectrum was obscured by other peaks or the resolution was insufficient for complete determination.

TABLE VII[a]

Substituent	Solvent	C-6	C-5	C-4	C-3 (axial)[b]	C-3 (equatorial)[b]
OH	DMSO-d_6	261.8	118.9	209	156.1 (10.0)	162.7 (7.0) [−17.2]
OCH_3	$CDCl_3$	267.5	119.0	212	152.0 (9.4)	176.0 (6.2) [−17.6]
$OCOCH_3$	$CDCl_3$	272.0	126.0	200	148.0 (10.4)	176.0 (5.0) [−17.0]
$OCOCH_3$	DMSO-d_6	265.0	117.0	207	153.1 (10.0)	160.1 (7.2) [−17.0]
OTos	$CDCl_3$	256.5	114.0	207	144.6 (10.0)	156.6 (6.2) [−17.0]

[a] Centers of multiplets, in cycles per second, for protons on indicated carbons. [b] Calculated chemical shift, followed by coupling constant with C-4 proton. The geminal coupling constant is given in brackets.

night at room temperature. The organic compounds were extracted into ethyl acetate and the acidic fractions were separated by washing the ethyl acetate solution with sodium bicarbonate solution. The remaining ethyl acetate solution containing the neutral fraction was concentrated to dryness and the oily residue was dissolved in benzene and chromatographed on 300 g of silica gel. Elution with 10% ethyl acetate in benzene gave, after evaporation of the solvent, 4.8 g (51.5% yield) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 102–103°. The analytical sample was prepared by recrystallization from acetone: mp 103–104°; ν_{KBr} 3235 (OH), 1602, 1592, 1503 (aromatic ring), 1687 (C=O), and 1255 cm^{-1} (CO). (Both the OH and C=O exhibit strong hydrogen bonding.)

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.63; H, 6.48.

B.—The solution of 10.0 g (0.05 mol) of 3,4-dihydrocoumarin-4-acetic acid (II)[4] in 100 ml of tetrahydrofuran was cooled to −10°. After the addition of 5.42 g (0.05 mol) of ethyl chloroformate the solution was stirred at −10° for 2 hr. Then 7.8 of sodium borohydride was added in small portions and the reaction mixture was stirred for 1 hr at room temperature and refluxed for 1 hr. The reaction mixture containing III was worked up in the same way as described in example A, yielding 4.4 g (47%) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 102–103°.

C.—To the solution of 2.06 g (0.01 mol) of 3,4-dihydrocoumarin-4-acetic acid (II)[4] in 150 ml of dry tetrahydrofuran was added 2 g (0.09 mol) of lithium borohydride. The mixture was refluxed for 16 hr, then the solvent was evaporated under reduced pressure, and 50 ml of 2 *N* hydrochloric acid solution was added to the precooled residue. The reaction mixture was worked up in the same way as described above, yielding 1.700 g (90%) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 102–103°.

4-Carbomethoxymethylcoumarin (VI).—To the suspension of 2.2 g (0.01 mol) of 3,4-dihydrocoumarin-4-acetic acid in dry ether was added a solution of diazomethane in ether at room temperature until the color of the diazomethane solution persisted. All the solid had dissolved at the end of the esterification procedure. The excess of diazomethane and the solvent was evaporated under reduced pressure and the residual oil, 3,4-dihydro-4-carbomethoxymethylcoumarin (V), was dissolved in a mixture of 44 ml of carbon tetrachloride and 8 ml of pentane. After the addition of 2.1 g (0.012 mol) of N-bromosuccinimide the reaction mixture was refluxed for 1 hr while illuminating with a 120-V photospot lamp. The solvent was evaporated under reduced pressure and the mixture dissolved in 25 ml of dimethylformamide, 2.5 g of lithium chloride was added, and the mixture was kept at 100° in a nitrogen atmosphere for 4 hr. The mixture was poured into 500 ml of cold water and the product was extracted into ethyl acetate. After evaporation of the solvent under reduced pressure, 1.87 g of crude product was obtained which was chromatographed on 100 g of silica gel. Elution with 10% ethyl acetate in benzene gave 1.78 g of 4-carbomethyoxymethylcoumarin, mp 124°. The analytical sample was crystallized from acetone: mp 124–125°; λ_{max} 313 mμ (ϵ 4700), 274 (ϵ 8250); ν_{KBr} 1750–1695 broad (ester C=O and lactone C=O), 1625 (C=C), 1610, 1563 (aromatic ring), 1250, 1225 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; 4.62. Found: C, 65.81; H, 4.64.

4-Methylcoumarin (VII). A. From 3,4-Dihydrocoumarin-4-acetic Acid.—To the solution of 500 mg (0.0025 mol) of 3,4-dihydrocoumarin-4-acetic acid in a mixture of 25 ml of carbon tetrachloride and 5 ml of pentane, 550 mg (0.003 mol) of N-bromosuccinimide was added and the mixture was refluxed for 40 min while illuminating with a 120-V photospot lamp. The solvent was evaporated under reduced pressure and the residue was dissolved in 10 ml of dimethylformamide. After the addition of 1 g of lithium chloride the mixture was kept at 100° in a mitrogen atmosphere for 4 hr. The mixture was poured into 300 ml of cold water and the product was extracted with ethyl acetate. After evaporation of the solvent 400 mg of crude product was obtained which was chromatographed on 250 g of silica gel. Elution with 20% ethyl acetate in benzene

gave 380 mg of 4-methylcoumarin, mp 80–81°. The analytical sample was crystallized from ether, then from ethanol: mp 82°; λ_{max} 310 mμ (ε 6000), 271 (ε 9900);[12] ν_{KBr} 1725 (C=O), 1618 (C=C), 1608, 1563 (aromatic ring), 1220 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.98; H, 5.11.

B. From 4-Carbomethyoxymethylcoumarin (VI).—To the solution of 100 mg of 4-carbomethoxymethylcoumarin in 10 ml of dioxane 5 ml of 20% aqueous hydrochloric acid was added and the solution was refluxed for 4 hr. The mixture was poured into 500 ml water, the product was extracted into ethyl acetate, and after evaporation of the solvent the residue was chromatographed on 50 g of silica gel. Elution with 20% ethyl acetate in benzene gave 65 mg of 4-methylcoumarin, identical with the above sample.

2-*o*-Tosyloxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (VIII).—To the solution of 750 mg (0.004 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) in 10 ml of pyridine 1 g (0.005 mole) of *p*-toluenesulfonyl chloride was added and the solution was allowed to stand overnight at room temperature. The solution was poured into ice containing 10 ml of 38% hydrochloric acid and the organic compounds were extracted into ethyl acetate. The ethyl acetate solution was washed with sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated under reduced pressure. The residual oil was chromatographed on 90 g of silica gel. Elution with 5% ethyl acetate in benzene and evaporation of the solvent gave 950 mg (70%) of 2-*o*-tosyloxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 130°. The analytical sample was crystallized from acetone: mp 130°; ν_{KBr} 1720 (C=O), 1618, 1582 (aromatic ring), 1360, 1150 (sulfonate), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{18}O_5S$: C, 62.41; H, 5.23; S, 9.25. Found: C, 62.40; H, 5.41; S, 9.48.

2-*o*-Acetoxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IX). To the solution of 960 mg (0.005 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone in 15 ml of pyridine 5 ml (0.05 mol) of acetic anhydride was added and the solution was allowed to stand at room temperature overnight. The solution was poured into ice containing 15 ml of 38% hydrochloric acid and the mixture was allowed to stand for 3 hr. The solid was removed by filtration, washed with water, and dried in the air. There was obtained 1.050 g (90%) of 2-*o*-acetoxyphenyl-4-hydroxybutane-1-carboxylic acid lactone. The analytical sample was crystallized from acetone: mp 137–138°; ν_{KBr} 1750 (C=O), 1695 (C=O), 1587, 1567 (aromatic ring), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.76; H, 5.87.

2-*o*-Methoxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (X).—To the solution of 1.0 g (0.005 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone in 100 ml of absolute ethanol 3 g of anhydrous potassium carbonate and 25 ml of methyl iodide was added and the mixture was refluxed for 20 hr with stirring. After the solvent was evaporated under reduced pressure, 2 *N* hydrochloric acid was added to the residue (to pH 1) and the organic compounds were extracted into ethyl acetate. The solvent was evaporated and the residual oil was chromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 360 mg of 2-*o*-methoxyphenyl derivative. Elution with 30% ethyl acetate in benzene gave 650 mg (65% recovery) of unchanged starting material. The 2-*o*-methoxyphenyl derivative was rechromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 332 mg of pure 2-*o*-methoxyphenyl-4-hydroxybutane-1-carboxylic acid lactone as an oil: ν_{film} 1730 (C=O), 1587, 1575 (aromatic ring), 1235 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.90, H, 6.92.

3,4-Dihydro-4-(β-trifluoroacetoxyethyl)coumarin (XI). A. From 2-*o*-Hydroxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IV).—The solution of 1.3 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) in 20 ml of trifluoroacetic anhydride was refluxed for 16 hr. The excess trifluoroacetic anhydride was removed under reduced pressure, 100 ml of benzene was added, and the solution was evaporated under reduced pressure to dryness. The residual oil was chromatographed on 100 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 1.894 g (96.5%) crystals: mp 61°; ν_{KBr} 1786 (C=O), 1613, 1587 (aromatic ring), 1220 (CO), 1150 cm^{-1} (CF).

Anal. Calcd for $C_{13}H_{11}O_4F_3$: C, 54.17; H, 3.85; F, 19.77. Found: C, 54.38; H, 3.83; F, 19.68.

B. From 3,4-Dihydro-4-(β-iodoethyl)coumarin.—To the solution of 622 mg of 3,4-dihydro-4-(β-iodoethyl)coumarin in 25 ml of trifluoroacetic acid 1.0 g of silver oxide was added and the mixture was heated at reflux with stirring in a nitrogen atmosphere for 16 hr. Most of the solvent was evaporated under reduced pressure, the residue poured into ice, and the product extracted into ethyl acetate. After evaporation of the solvent the residue was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 510 mg (85% yield) of 3,4-dihydro-4-(β-trifluoroacetoxyethyl)coumarin, identical with the compound obtained as described above.

3,4-Dihydro-4-(β-chloroethyl)coumarin (XII). A. From 2-*o*-Hydroxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IV).—To the solution of 576 mg (0.003 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone in 150 ml benzene, 1.8 g (0.015 mol) of thionyl chloride was added and the solution was heated at reflux for 3 hr. The solvent was evaporated under reduced pressure and 100 ml of benzene was added and evaporated under reduced pressure. The residual oil was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 582 mg (92%) of 3,4-dihydro-4-(β-chloroethyl)coumarin, mp 61°. The analytical sample was crystallized from pentane: mp 61°; ν_{KBr} 1724 (C=O), 1587, 1575 (aromatic ring), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.71; H, 5.26; Cl, 16.83. Found: C, 62.90; H, 5.09; Cl, 16.75.

B. From 3,4-Dihydro-4-(β-trifluoroacetoxyethyl)coumarin (XI).—To the solution of 288 mg of 3,4-dihydro-4-(β-trifluoroacetoxyethyl)coumarin in 25 ml of dimethylformamide 2.0 g of lithium chloride was added. The mixture was held at 100° in a nitrogen atmosphere for 4 hr. The solution was cooled and poured into ice, the organic compound extracted into ethyl acetate, the solvent evaporated, and the residual oil chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 203 mg (96%) of 3,4-dihydro-4-(β-chloroethyl)coumarin, identical with the compound obtained as described under A.

3,4-Dihydro-4-(β-bromoethyl)coumarin (XIII).—The solution of 576 mg of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) in 25 ml of chloroform was cooled to 0°. At this temperature hydrogen bromide gas was introduced until the solution became saturated with the gas. The solution was allowed to stand at 0° overnight. The solution was diluted with ether and poured into ice, and the product was extracted into ether. The combined organic solution was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene gave 758 mg (99% yield) of crystals, mp 63–64°. The analytical sample was crystallized from pentane: mp 65°; ν_{KBr} 1770 (C=O), 1610, 1580 (aromatic ring), 1220 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{11}O_2Br$: C, 51.78; H, 4.44; Br, 31.33. Found: C, 51.96; H, 4.39; Br, 31.60.

3,4-Dihydro-4-ethylcoumarin (XIV).—To the solution of 333 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 25 ml of acetic acid 100 mg of platinum dioxide was added and the mixture was hydrogenated in a Parr hydrogenator overnight at 45 psi. The catalyst was filtered off and the solution was diluted with benzene. The solution was washed with water, sodium bicarbonate solution, and water. The benzene solution was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give an oil. This was chromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 216 mg (94%) of oil, which contained no bromine. The structural assignment was made on the basis of the nmr spectrum (Table V).

3,4-Dihydro-4-(β-iodoethyl)coumarin (XV).—To the solution of 500 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 20 ml of xylene and 10 ml of acetic acid 300 mg of sodium iodide was added and the mixture was stirred at reflux temperature in an atmosphere of nitrogen for 16 hr. The mixture was added to 300 g of ice, 300 ml of aqueous saturated sodium sulfate solution was added, and the product was extracted into ethyl acetate. The combined organic layer was dried over

sodium sulfate and the solvent was evaporated under reduced pressure. The residual oil was chromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 592 mg (100% yield) of 3,4-dihydro-4-(β-iodoethyl)coumarin as an oil: ν_{film} 1770 (C=O), 1618, 1565 (aromatic ring), 1220 cm^{-1} (CO). The compound gave a positive halogen test.

3,4-Dihydro-4-(β-hydroxyethyl)coumarin (XVI).—To the solution of 510 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 25 ml of dimethylformamide 550 mg of silver carbonate was added and the mixture was kept at 100° with stirring in a nitrogen atmosphere for 16 hr. The mixture was poured into ice containing 2 *N* hydrochloric acid, the product was extracted into ethyl acetate, the solvent was evaporated under reduced pressure, and the residue was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene gave 332 mg (86% yield) of 3,4-dihydro-4-(β-hydroxyethyl)coumarin as an oil, which showed a single spot on a tlc plate: ν_{film} 3580 (OH), 1770 (C=O), 1610, 1580 (aromatic ring), 1220 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; Found: C, 68.83; H, 6.20.

3,4-Dihydro-4-(β-acetoxyethyl)coumarin (XVII).—To the solution of 510 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 25 ml of glacial acetic acid 510 mg of silver oxide was added and the mixture was kept boiling with stirring in a nitrogen atmosphere for 16 hr. The mixture was cooled, diluted with ethyl acetate, and poured into a sodium bicarbonate solution. The product was extracted into ethyl acetate, the solvent evaporated under reduced pressure, and the residue chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene gave 444 mg (95% yield) of 3,4-dihydro-4-(β-acetoxyethyl)coumarin, as an oil, which showed a single spot on a tlc plate; ν_{film} 1776 (C=O), 1745 (C=O), 1610, 1580 (aromatic ring), 1240 cm^{-1} (CO).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.77; H, 6.06.

Ortho Substituted Phenyl-2-hydroxyethyl-N-alkylhydrocinnamamides (XVIII). General Procedure.—The solution of *o*-hydroxy- (or tosyloxy-) phenyl-4-hydroxybutane-1-carboxylic acid lactone in a tenfold volume of freshly distilled primary or secondary amine was kept at 100° in an atmosphere of nitrogen for 16 hr. The solution was diluted with ethyl acetate, poured into ice containing hydrochloric acid, and the acidic solution was extracted with ethyl acetate. The solvent was evaporated and the oily residue was chromatographed on a 100-weight silica gel column. Elution with 30% ethyl acetate in benzene and evaporation of the solvent gave an oily product which was crystallized.

a. *o*-Hydroxy-2-hydroxyethyl-N-piperidylhydrocinnamamide.—From 1.0 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) and piperidine there was obtained 1.257 g (82% yield) of product, which was crystallized from acetone–hexane. The analytical sample was crystallized from ether: mp 99–100°; ν_{KBr} 3330 (OH), 1603 (CON=), 1235 cm^{-1} (CO).

Anal. Calcd for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.01; H, 8.55; N, 4.99.

b. *o*-Tosyloxy-2-hydroxyethyl-N-piperidylhydrocinnamamide.—From 1.0 g of 2-*o*-tosyloxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (VIII) and piperidine there was obtained 1.205 g (96% yield) of product, which was crystallized from ether: mp 108°; ν_{KBr} 3300 (OH), 1603 (CON=), 1235 (CO), 1360, 1150 cm^{-1} (sulfonate).

Anal. Calcd for $C_{23}H_{29}O_5NS$: C, 64.01; H, 6.77; N, 3.24; S, 7.43. Found: C, 63.80, H, 6.59; N, 3.53; S, 7.52.

c. *o*-Hydroxy-2-hydroxyethyl-N-benzylhydrocinnamamide.—From 1.0 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) and benzylamine there was obtained 1.420 g (91% yield) of product, which was crystallized from acetone–hexane. The analytical sample was crystallized from tetrahydrofuran: mp 132–132.5°; ν_{KBr} 3509 (NH), 3333 (OH), 1618 (CONH), 1587, 1563 (aromatic ring), 1225 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.56; H, 7.07; N, 4.64.

d. *o*-Hydroxy-2-hydroxyethyl-N-cyclohexylhydrocinnamamide.—From 1.0 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) and cyclohexylamine there was obtained 1.257 g (83% yield) of product, which was crystallized from pentane. The analytical sample was prepared from ether: mp 128–129°; ν_{KBr} 3390 (NH), 3280 (OH), 1600 (CONH), 1563, 1538 (aromatic ring), 1235 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.05; H, 8.60; N, 4.62.

4-Carboalkylamidomethylchromans (XIX). General Procedure.—The solution of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in a 10-fold volume of freshly distilled primary or secondary amine was kept at 100° in an atmosphere of nitrogen for 16 hr. The solution was diluted with ethyl acetate and poured into ice containing hydrochloric acid; the acidic solution was extracted with ethyl acetate. The solvent was evaporated and the oily residue was chromatographed on a 100-fold weight silica gel column. Elution with 30% ethyl acetate in benzene and evaporation of the solvent furnished a solid product, which was crystallized from different solvents.

a. 4-Carbobenzylamidomethylchroman.—From 300 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) and benzylamine there was obtained 280 mg (83% yield) of product, which was crystallized from ether: mp 201–202°; ν_{KBr} 3175 (NH), 1626 (CONH), 1585 (aromatic ring), 1220 (CO), 1070 cm^{-1} (COC).

Anal. Calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.65; H, 6.77; N, 5.23.

b. 4-Carbohexylamidomethylchroman.—From 180 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin(XIII) and cyclohexylamine there was obtained 180 mg (93% yield) of product, which was crystallized from ether: mp 147–148°; ν_{KBr} 3322 (NH), 1618 (CONH), 1600, 1567 (aromatic ring), 1220 (CO), 1078 cm^{-1} (COC).

Anal. Calcd for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.70; H, 8.69; N, 4.97.

c. 4-Carbopiperidylmethylchroman.—From 400 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) there was obtained 300 mg (73% yield) of product, which was crystallized from ether: mp 98°; ν_{KBr} 1626 (CON=), 1610, 1585 (aromatic ring), 1220 (CO), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.36; H, 8.39; N, 5.50.

d. 4-Carbodiethylamidomethylchroman.—From 280 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) there was obtained 200 mg of syrupy product which could not be crystallized: ν_{film} 1634 (CON=), 1610, 1575 (aromatic ring), 1220 (CO), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.60; H, 8.78; N, 5.45.

3,4-Dihydro-4-(β-phenylaminoethyl)coumarin.—The solution of 500 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 10 ml of freshly distilled aniline was kept at 110° in an atmosphere of nitrogen for 20 hr. The excess aniline was removed by evaporation under reduced pressure and the remaining oil was dissolved in benzene and chromatographed on 90 g of silica gel. The column was washed with 500 ml of benzene. Elution with ethyl acetate after evaporation of the solvent gave 425 mg (82.5%) of 3,4-dihydro-4-(β-phenylaminoethyl)coumarin, mp 222°. The analytical sample was crystallized from ether: mp 222–223°; ν_{KBr} 3333 (NH), 1639 (CONH), 1610, 1575 (aromatic ring), 1220 (CO), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.51; H, 6.63; N, 5.25.

4-Carbohydroxymethylchroman (Chroman-4-acetic Acid) (XXI).—The solution of 510 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 50 ml of methanol containing 500 mg of potassium hydroxide was kept at reflux in a nitrogen atmosphere for 16 hr. The solution was concentrated under reduced pressure to a small volume and diluted with ethyl acetate; the solution was washed with dilute hydrochloric acid. Evaporation of the solvent gave an oil, which was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 366 mg (95%), mp 90° of 4-carbohydroxymethylchroman, free of halogen. The analytical sample was crystallized from ether–hexane: mp 91–92°; ν_{KBr} 3125 broad (COOH), 1695 (acid) 1587, 1563 (aromatic ring), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.81; H, 6.47.

4-Carbomethoxymethylchroman (XXII).—To the solution of 1.0 g of 4-carbohydroxymethylchroman (XXI) in 100 ml of ether was added a solution of diazomethane in ether at room temperature until the color of the diazomethane solution persisted. The excess of diazomethane and the solvent was

evaporated under reduced pressure and the residue was purified on a 100 g of silica gel column. Elution with 10% ethyl acetate in benzene and evaporation of the solvent gave 1075 mg (100% yield) of 4-carbomethoxymethylchroman as an oil: ν_{film} 1740 (C=O), 1610, 1585 (aromatic ring), 1075 cm^{-1} (COC).

Registry No.—IV, 10513-48-1; VI, 15364-61-1; VII, 607-71-6; VIII, 15364-63-3; IX, 15364-64-4; X, 15364-65-5; XI, 15364-66-6; XII, 15364-67-7; XIII, 15364-68-8; XIV, 15523-38-3; XV, 15364-69-9; XVI, 15364-70-2; XVII, 15364-71-3; XVIIIa, 15364-72-4; XVIIIb, 15364-73-5; XVIIIc, 15364-74-6; XVIIId, 15364-75-7; XIXa, 15364-76-8; XIXb, 15364-77-9; XIXc, 15364-78-0; XIXd, 15364-79-1; XX, 15364-80-4; XXI, 5655-26-5; XXII, 15364-82-6.

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Synthesis of L-α-Methyldopa from Asymmetric Intermediates

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Two procedures for the synthesis of L-α-methyldopa from asymmetric intermediates are described. The substrates for the resolution and racemization processes are DL-α-amino-α-vanillylpropionitrile and DL-α-acetamido-α-vanillylpropionitrile. Hydrolysis of the L isomer yields L-α-methyldopa in high yield.

The hypotensive activity of α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa)[1] (VI) has been shown to reside only in the L isomer.[2] To eliminate the therapeutically impotent D isomer, DL-α-methyldopa has been resolved by conventional methods,[3] and, more recently, by a selective crystallization technique not involving a resolving agent.[4] However, resolution at the amino acid stage results in equal production of the unwanted D isomer which cannot be racemized by usual means because of the absence of an α hydrogen. Practical utilization of the D isomer has been limited to degradation to 3,4-dihydroxyphenylacetone followed by resynthesis of the amino acid.[5]

The asymmetry of the molecule is introduced on formation of the α-aminonitrile or hydantoin intermediates. Of these two intermediates, the α-aminonitrile, being a base[6] and formed in an equilibrium reaction,[7] is uniquely suited for both resolution[8,9] and racemization.[10] The resolutions hitherto reported have all been impaired by the facile hydrolysis of the salts of α-aminonitriles with weak acids. This leads to irreversible decomposition of the aminonitriles to the parent ketones and ammonia, which is captured by the resolving agent.

The optical instability of α-aminonitriles suggested that, in addition to the two general types of resolution process developed for DL-α-methyldopa, it would be possible to develop an asymmetric transformation,[11] initiated in this case by seeding with optically active α-aminonitrile which would result in the crystallization of only the desired L isomer in greater than 50% yield. This ultimate process requires not only a preliminary resolution to produce the seeds, but a favorable solubility relationship between the optically active forms, a rapid rate of crystal growth on the seed bed relative to nucleation of the inactive form, and, finally, a rate of racemization faster than the rate of crystallization.[12]

This approach was tested on the α-aminonitrile II prepared from 3-methoxy-4-hydroxyphenylacetone I (Scheme I). The initial resolution experiments[13] were frustrated by the tendency of its salts to dissociate. However, continued screening of the salts of II with strong acids, using the phase solubility analysis technique,[14] revealed that the *d*-10-camphorsulfonate could be resolved in dioxane, thanks to the formation of a crystalline solvate, $[\alpha]_D$ 15.6°. The absolute configuration and purity were determined by hydrolysis to D-α-methyldopa of known configuration.[3] The other enantiomer of II was obtained *via* the *l*-10-camphorsulfonate[15] dioxanate V, $[\alpha]_D$ −14.7°.

The optically active α-aminonitrile L-II, $[\alpha]_D$ 8.90°, was liberated from its salt with ammonia in ether. It melted completely at 86–88°, then immediately crystallized, and remelted at 125–128°; the melting point remained at 125° thereafter. Hydrogen cyanide

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